



NTP

National Toxicology Program

Draft OHAT Approach Part 2 Confidence in the Body of Evidence Through Integrating the Evidence

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Web-Based Informational Meeting
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Draft OHAT Approach for Systematic Review and Evidence Integration for Literature-Based Health Assessments

This Presentation will focus on Steps 5-7

Step 1: Prepare topic

Step 2: Search for and select studies

Step 3: Extract data from studies

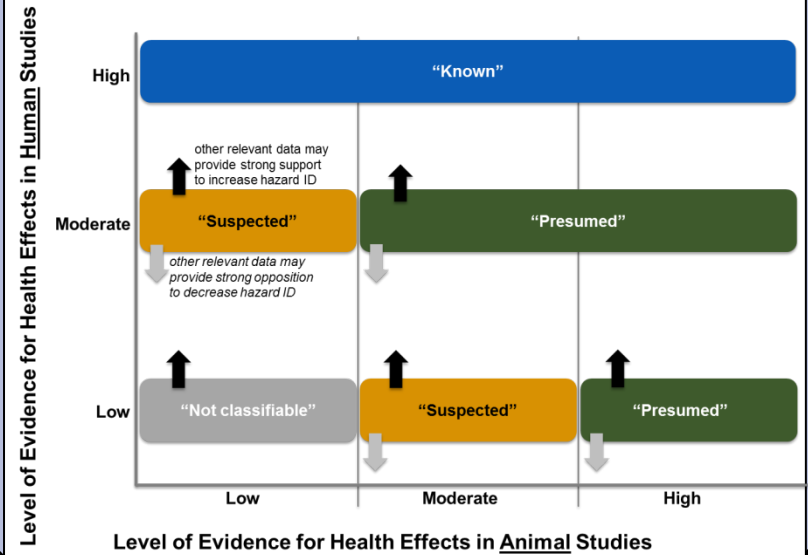
Step 4: Assess individual study quality

Step 5: Rate confidence in body of evidence

| Initial Confidence by Key Features of Study Design | Factors Decreasing Confidence | Factors Increasing Confidence | Confidence in the Body of Evidence |
|--|---|---|------------------------------------|
| High (++++) 4 Features | <ul style="list-style-type: none"> Risk of Bias | <ul style="list-style-type: none"> Large Magnitude of Effect | High (++++) |
| Moderate (+++) 3 Features | <ul style="list-style-type: none"> Unexplained Inconsistency | <ul style="list-style-type: none"> Dose Response | Moderate (+++) |
| Low (++) 2 Features | <ul style="list-style-type: none"> Indirectness | <ul style="list-style-type: none"> All Plausible Confounding <ul style="list-style-type: none"> Studies report an effect and residual confounding is toward null Studies report no effect and residual confounding is away from null | Low (++) |
| Very Low (+) ≤1 Features | <ul style="list-style-type: none"> Imprecision Publication Bias | <ul style="list-style-type: none"> Consistency <ul style="list-style-type: none"> Across animal models or species Across dissimilar populations Across study design types Other <ul style="list-style-type: none"> e.g., particularly rare outcomes | Very Low (+) |

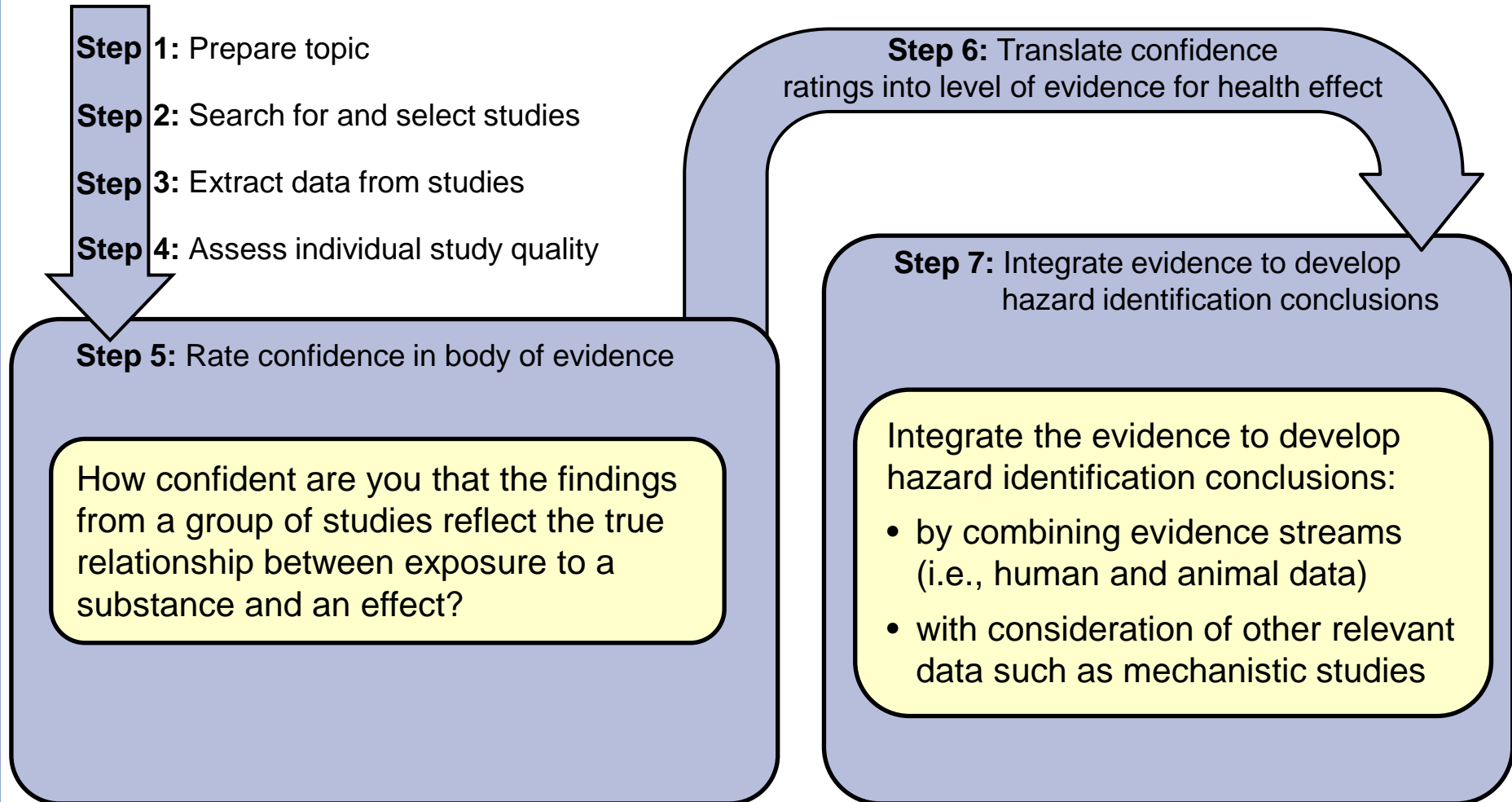
Step 6: Translate confidence ratings into level of evidence for health effect

Step 7: Integrate evidence to develop hazard identification conclusions



Draft OHAT Approach for Systematic Review and Evidence Integration for Literature-Based Health Assessments

This Presentation will focus on Steps 5-7



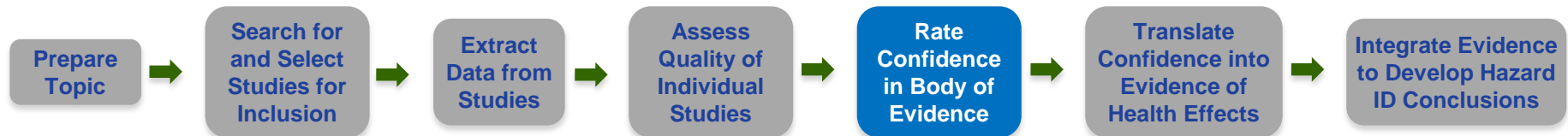
Step 5: Rate Confidence in the Body of Evidence

- **Confidence Rating**

- How confident are you that findings from a group of studies reflect the true relationship between exposure to a substance and an effect?

- **Existing Methods**

- The GRADE approach is a widely accepted method for rating confidence in a body of evidence
 - No guidance for animal studies
 - No guidance for *in vitro* studies
 - All observational human studies are given the same initial low quality (e.g., case-report = prospective cohort study)



Why GRADE?

- Developed by broad group of international guideline developers in the area of healthcare
- Clear presentation of elements considered for downgrading or upgrading confidence in body of evidence
 - Framework for documenting scientific judgment decisions
 - Elements cover Bradford Hill causality considerations
 - Practitioners engage in ongoing methods development
- Endorsed and used by over 70 organizations
- Consistent with DHHS sister agencies
 - Conceptually similar to AHRQ model
 - Supported by parts of CDC for healthcare recommendations



Step 5: Rate Confidence in the Body of Evidence



- **Confidence Rating** (human and animal data separately)
 - Indicates confidence that findings from the body of evidence reflects the true relationship between exposure to a substance and an effect
 - **Initial Confidence**
 - On an outcome basis
 - Determined by key study design features

| Initial Confidence |
|--------------------|
| High |
| Moderate |
| Low |
| Very Low |

Key Features

- Controlled exposure
- Exposure prior to outcome
- Individual outcome data
- Comparison group used

Reflect the ability of study design to address confidence that exposure preceded and was associated with outcome

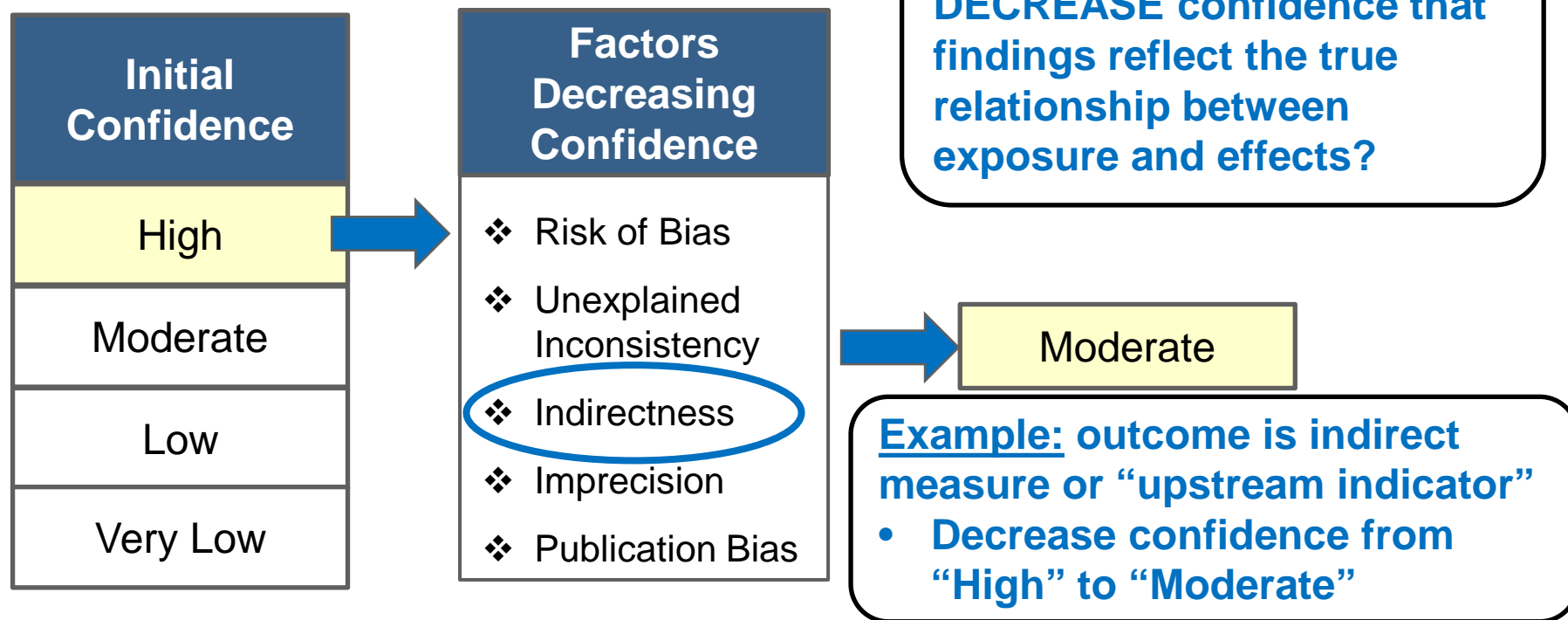
Example:

- Well conducted experimental studies will have all 4 key features
- Therefore “High” initial confidence

Step 5: Rate Confidence in the Body of Evidence



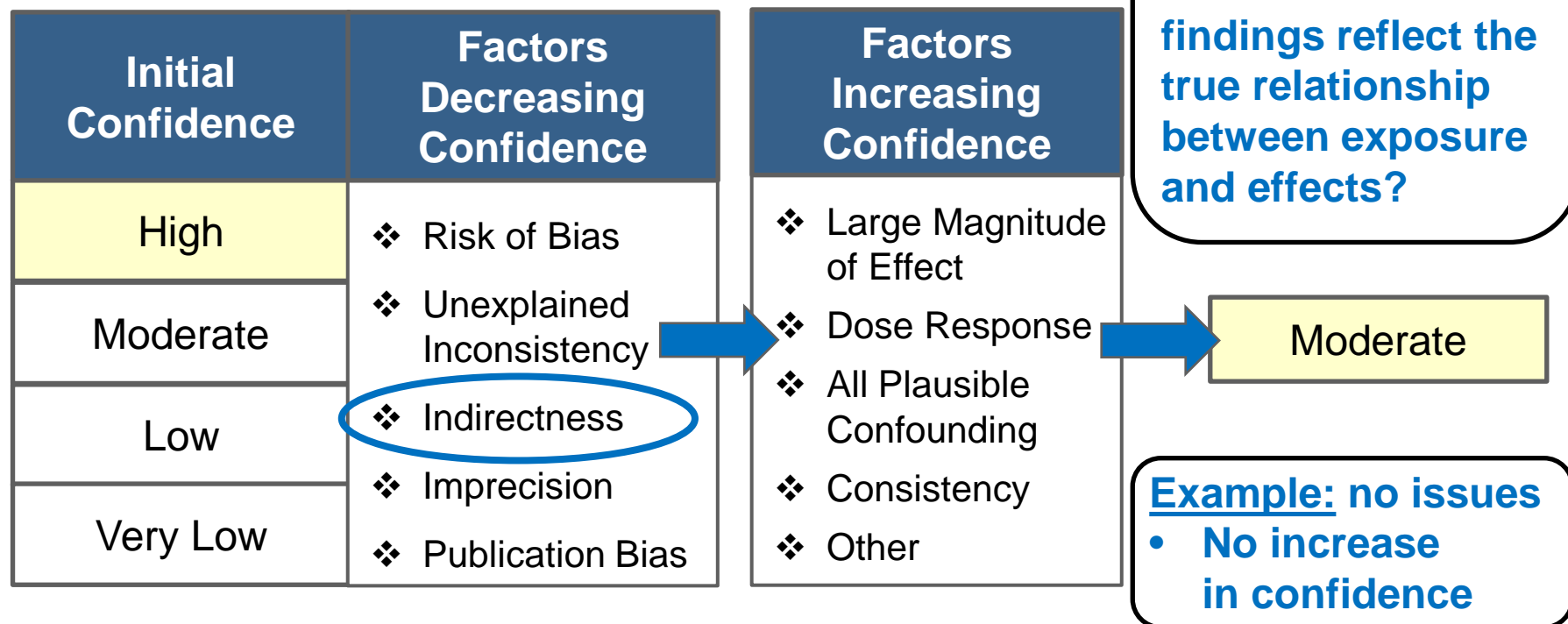
- **Confidence Rating** (human and animal data separately)
 - Indicates confidence that findings from the body of evidence reflects the true relationship between exposure to a substance and an effect
 - **Initial Confidence**
 - **Factors Decreasing Confidence**



Step 5: Rate Confidence in the Body of Evidence



- **Confidence Rating** (human and animal data separately)
 - Indicates confidence that findings from the body of evidence reflects the true relationship between exposure to a substance and an effect
 - **Initial Confidence**
 - **Factors Decreasing Confidence**
 - **Factors Increasing Confidence**



Step 5 Schematic: Adaptations to Address Breadth of Data Relevant for Environmental Health Questions



Initial confidence set by study design features in OHAT Approach (stratifies observational studies)

| Initial Confidence by Key Features of Study Design | Factors Decreasing Confidence | Factors Increasing Confidence | Confidence in the Body of Evidence |
|--|--|---|---|
| High (++++) 4 Features | <ul style="list-style-type: none"> ❖ Risk of Bias ❖ Unexplained Inconsistency ❖ Indirectness ❖ Imprecision ❖ Publication Bias | <ul style="list-style-type: none"> ❖ Large Magnitude of Effect ❖ Dose Response ❖ All Plausible Confounding <ul style="list-style-type: none"> • Studies report an effect and residual confounding is toward null • Studies report no effect and residual confounding is away from null ❖ Consistency <ul style="list-style-type: none"> • Across animal models or species • Across dissimilar populations • Across study design types ❖ Other <ul style="list-style-type: none"> e.g., particularly rare outcomes | High (++++) Moderate (+++) Low (++) Very Low (+) |

Features

- Controlled exposure
- Exposure prior to outcome
- Individual outcome data
- Comparison group used

OHAT added consistency across breadth of data

Example Guidance in Protocols: When to Downgrade for Unexplained Inconsistency

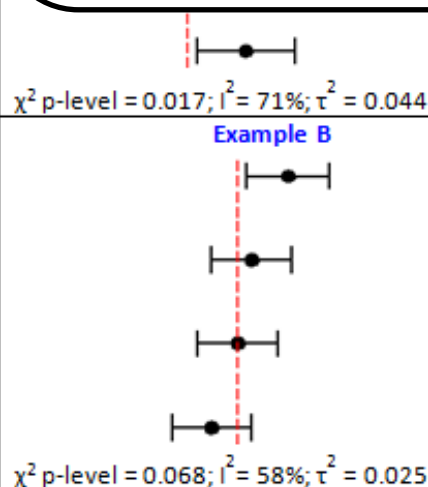
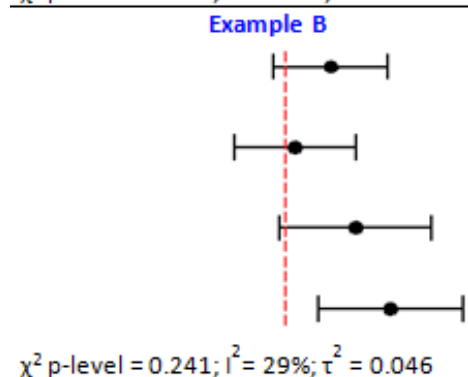
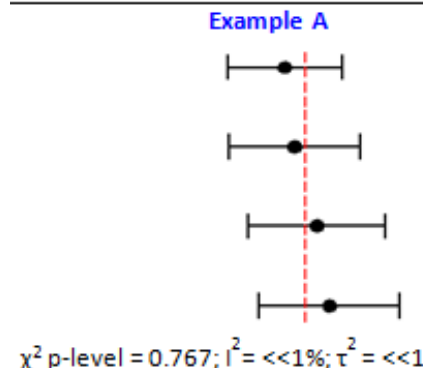
Table 15. Factors to consider when considering consistency of results

| No downgrade |
|---|
| <ul style="list-style-type: none"> - Point estimates similar - Confidence intervals overlap - Statistical heterogeneity is non-significant - I^2 of $\leq 50\%$ |

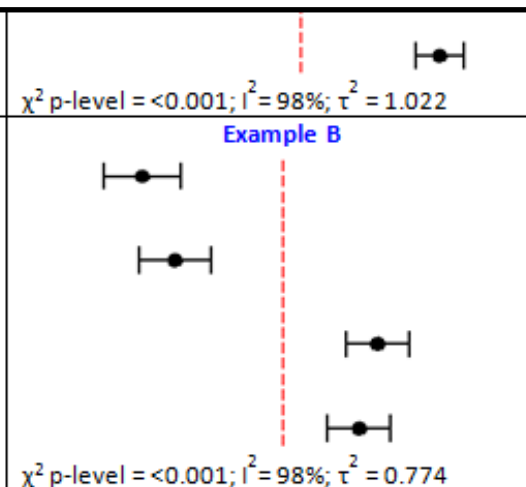
Factors to Consider for No Downgrade

- Point estimates similar
- Confidence intervals overlap
- Statistical heterogeneity non-significant ($p \geq 0.1$)
- I^2 of $\leq 50\%$

Example figures



χ^2 p-level = 0.068; I^2 = 58%; τ^2 = 0.025

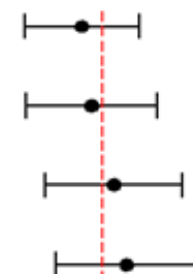
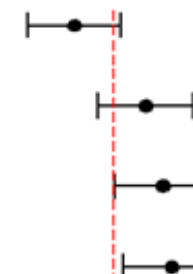
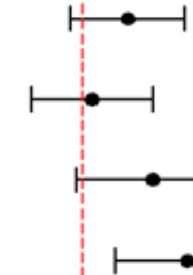
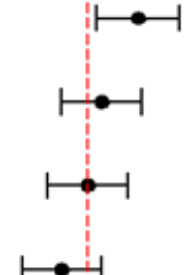
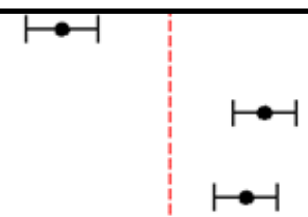


χ^2 p-level = <0.001; I^2 = 98%; τ^2 = 0.774

*protocol also includes guidance on when we might conduct a quantitative data synthesis

Example Guidance in Protocols: When to Downgrade for Unexplained Inconsistency

Table 15. Factors to consider when considering consistency of results

| No downgrade | One level downgrade (serious) | Two level downgrade (very serious) |
|---|--|--|
| <ul style="list-style-type: none"> Point estimates similar Confidence intervals overlap Statistical heterogeneity is non-significant I^2 of $\leq 50\%$ | <ul style="list-style-type: none"> Point estimates vary Confidence intervals show minimal overlap Statistical heterogeneity has low p-value I^2 of $>50\%$ to 75% | |
| <p>Example A</p>  <p>χ^2 p-level = 0.767; $I^2 = <<1\%$; $\tau^2 = <<1$</p> | <p>Example A</p>  <p>χ^2 p-level = 0.017; $I^2 = 71\%$; $\tau^2 = 0.044$</p> | |
| <p>Example B</p>  <p>χ^2 p-level = 0.241; $I^2 = 29\%$; $\tau^2 = 0.046$</p> | <p>Example B</p>  <p>χ^2 p-level = 0.068; $I^2 = 58\%$; $\tau^2 = 0.025$</p> |  <p>χ^2 p-level = <0.001; $I^2 = 98\%$; $\tau^2 = 0.774$</p> |

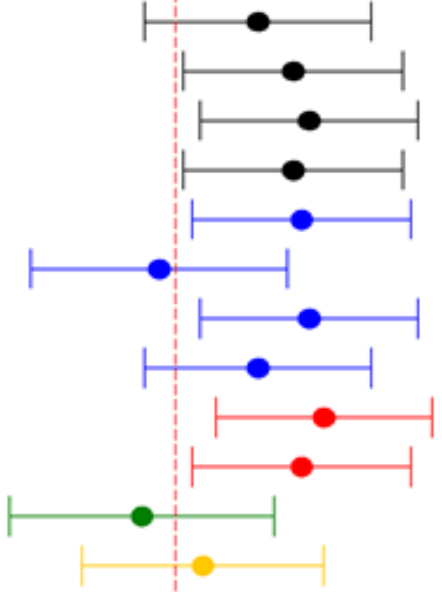
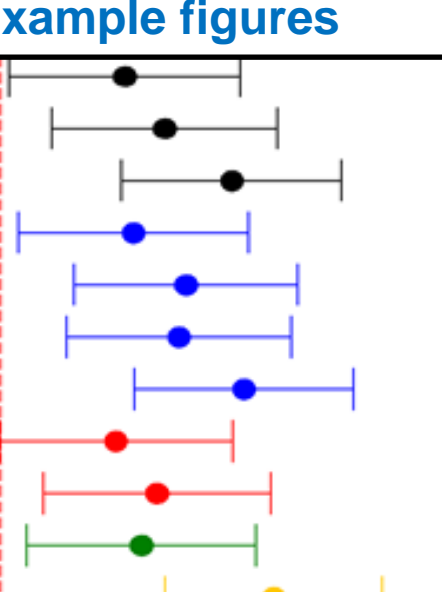
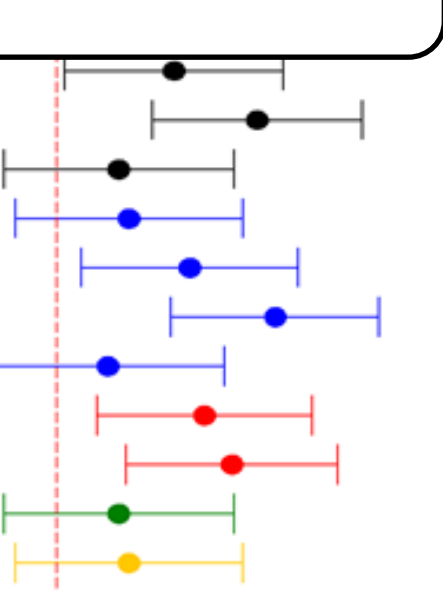
Factors to Consider to Downgrade 1 Level

- Point estimates vary
- Confidence intervals show minimal overlap
- Statistical heterogeneity has low p-value ($p < 0.1$)
- I^2 of $>50\%$ to 75%
- Example figures

*protocol also includes guidance on when we might conduct a quantitative data synthesis

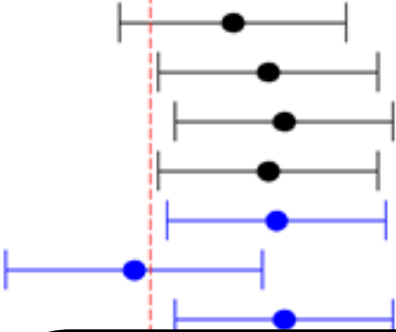
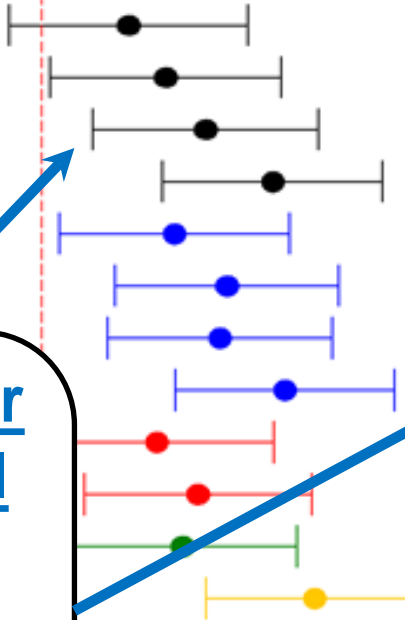
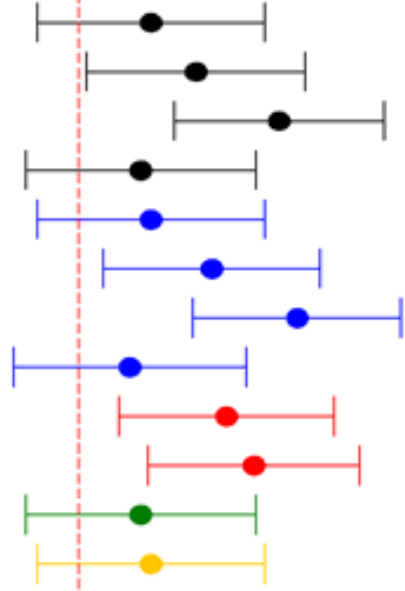
Example Guidance in Protocols: When to Upgrade for Dose Response Gradient

Table 19. Conceptual examples of upgrade decisions for evidence of dose response gradient

| no upgrade | <h2>Factors to Consider for No Upgrade</h2> <ul style="list-style-type: none"> No evidence of dose response Example figures | |
|--|---|--|
| Example A, findings sorted by study and then dose or exposure level (low to high) | | |
|  |  |  |

Example Guidance in Protocols: When to Upgrade for Dose Response Gradient

Table 19. Conceptual examples of upgrade decisions for evidence of dose response gradient

| no upgrade | upgrade +1 (monotonic) | upgrade +1 (non-monotonic) ¹ |
|---|---|--|
| Example A, findings sorted by study and then dose or exposure level (low to high) | Example B, findings sorted by study and then dose or exposure level (low to high) | Example C, findings sorted by study and then dose or exposure level (low to high) |
|  |  |  |

Factors to Consider to Upgrade 1 Level

- Monotonic
- Non- monotonic
- Evidence of dose response within a study
- Evidence of dose response across studies

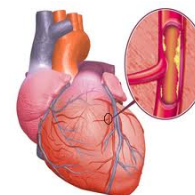
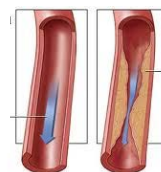
Reaching Final Confidence Conclusions on Human and Animal Studies



- Conclusions are based on the evidence with the highest confidence rating when considering across study designs and multiple outcomes
- **Across biologically-related outcomes**
 - **First:** rate confidence in individual outcomes
 - **Then:** re-evaluate confidence conclusion for combined outcomes
 - The overall confidence conclusion for a combined outcome can differ from (e.g., be higher than) the individual outcome ratings

Example:

Blood Pressure
Cardiovascular disease
Cardiovascular mortality



- **Note:** If body of evidence has “Very Low” confidence, it is not used to develop hazard ID conclusions in steps 6 and 7

Confidence in Other Relevant Studies: Assessment of Biological Plausibility

Factors considered when evaluating the support for biological plausibility provided by *in vitro*, cellular, genomic, or mode of action data



Strong Support¹

Weak Support

- *Relevance of biological process or pathway to human health*
- *Consistency*
- *Relevance of concentration*
- *Potency*
- *Dose response*
- *Publication bias*

Factors considered parallel elements used to evaluate confidence in the other data streams

A conclusion of “strong” support for biological plausibility requires that most elements are met

Step 6: Translate Confidence Ratings into Level of Evidence for Health Effects

- **Level of evidence for health effects** conclusions reflect
 - The overall confidence in the association between exposure to a substance and a given outcome, and
 - The direction of the effect (toxicity or no toxicity)

| Confidence in the Body of Evidence | Direction (effect or no effect) | Level of Evidence for Health Effect |
|------------------------------------|---------------------------------|-------------------------------------|
| (+++++) High | Health effect | High |
| (+++)+ Moderate | Health effect | Moderate |
| (++) Low | Health effect | Low |
| (+++++) High | No effect | Evidence of no health effect |
| (+++)+ Moderate | No effect | Inadequate |
| (++) Low | No effect | Inadequate |

Note: descriptors are applied separately to human and experimental animal evidence



Step 7: Integrate Evidence to Develop Hazard Identification Conclusions



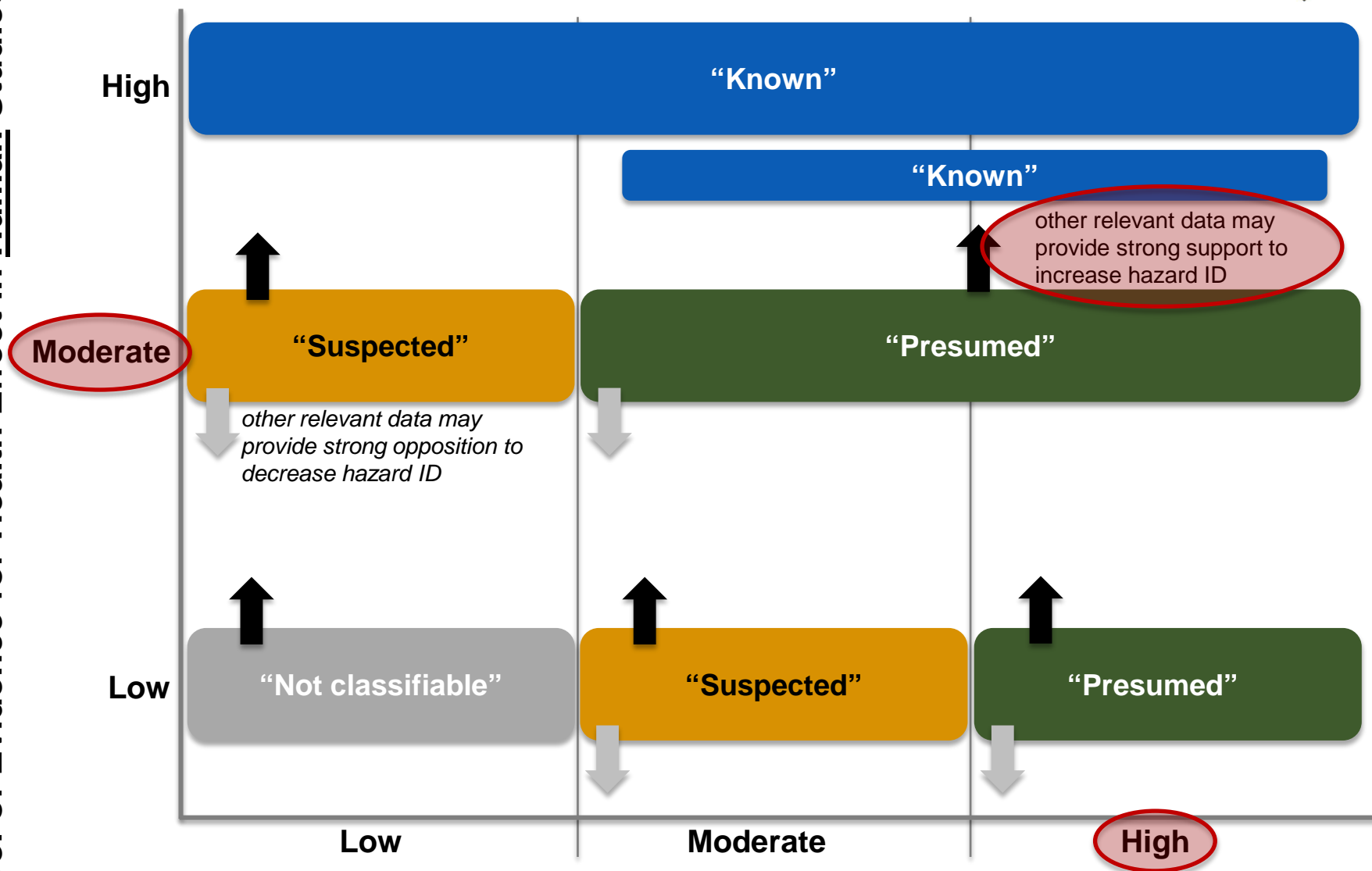
- **Integrate evidence** by combining evidence streams to reach one of four overall hazard identification conclusions
 - **Known** to be a hazard to humans
 - **Presumed** to be a hazard to humans
 - **Suspected** to be a hazard to humans
 - **Not classifiable** to be a hazard to humans
- Two part process for integrating the evidence
 - Consider human evidence and animal evidence together
 - Consider impact of other relevant data
 - e.g., mechanistic, *in vitro*, or upstream indicator data



Integrate Evidence to Develop Hazard ID Conclusions



Level of Evidence for Health Effect in Human Studies



Level of Evidence for Health Effects in Animal Studies

Assessment of Biological Plausibility Provided by Other Relevant Studies: PFOA/PFOS and Immunotoxicity

- **Consider upgrading the hazard ID**

If other relevant data provide strong support for biological plausibility of the relationship between exposure and the health effect

- To provide support, the mechanistic or *in vitro* data must support biological plausibility of **observed immune outcomes** from human epidemiology or *in vivo* animal studies
- It is also envisioned that strong evidence for a relevant biological process from mechanistic or *in vitro* data could result in a conclusion of “suspected” **in the absence of human epidemiology or *in vivo* animal data**

Assessment of Biological Plausibility Provided by Other Relevant Studies: PFOA/PFOS and Immunotoxicity

Factors considered when evaluating the support for biological plausibility provided by *in vitro*, cellular, genomic, or mode of action data



More detail and examples provided in the protocol

Strong Support¹

- **Relevance of biological process or pathway to human health**
generally accepted as relevant (e.g., myelotoxicity or bone marrow toxicity)
- **Consistency**
consistency across multiple studies (preferably in more than 2 in different model systems for the same biological pathway)
- **Relevance of concentration**
physiologically relevant or “low” concentration effects (e.g., mean of 3-5ng/ml PFOA and 9–30 ng/ml PFOS in the US population 1999-2010 ([CDC 2012](#)) range of 17-5100 ng/ml PFOA and 37-3490 ng/ml PFOS in occupationally exposed adults)
- **Potency**
magnitude of response
- **Dose response**
displays expected dose
- **Publication bias**
undetected

Consistency still applies in absence of *in vivo* data, analogous to other data streams

Consistency

- Within context of observed *in vivo* immune outcomes
 - IgE supports sensitization
 - IgE does not support NK
- Stronger if data provide information on multiple steps along the relevant biological pathway
- Also applies to repeatability within the same assay across studies

Causality Considerations in draft OHAT Approach

| Hill Considerations | Consideration in the OHAT Approach |
|--------------------------------|--|
| Strength | <ul style="list-style-type: none"> • upgrading the confidence in the body of evidence for <i>large magnitude of effect</i> • downgrading confidence for imprecision |
| Consistency | <ul style="list-style-type: none"> • upgrading confidence in the body of evidence for <ul style="list-style-type: none"> • <i>consistency across study types,</i> • <i>consistency across dissimilar populations</i> • <i>consistency across animal species or models</i> • integrating the body of evidence among human, animal, and other relevant data • downgrading confidence in the body of evidence for <i>unexplained inconsistency</i> |
| Temporality | <ul style="list-style-type: none"> • the <i>initial confidence ratings</i> by study design, for example experimental studies are rated “High” because of the increased confidence that exposure preceded outcome |
| Biological gradient | <ul style="list-style-type: none"> • upgrading the confidence in the body of evidence for a <i>dose-response</i> relationship |
| Biological plausibility | <ul style="list-style-type: none"> • in examining non monotonic dose-response relationships • in developing confidence conclusions across biologically related outcomes • other relevant data that inform plausibility are considered in integrating the body of evidence • downgrading the confidence in the body of evidence for indirectness |
| Experimental evidence | <ul style="list-style-type: none"> • the initial confidence ratings by study design • downgrading for risk of bias |

Next Steps

- Framework is currently available for public comment
 - Released publically February 25, 2013
 - For more files and details see <http://ntp.niehs.nih.gov/go/38673>
 - **Public comment period ends June 11, 2013**
- Two case studies to assess and refine methods
 - Protocols illustrate the application of this framework
 - BPA exposure and obesity
 - PFOA or PFOS exposure and immunotoxicity
 - Released publically April 9, 2013
- Careful consideration of comments from public and at NTP Board of Scientific Councilors Meeting June 25, 2013
- Release updated guidance
 - Expect to be updated periodically, e.g., new best practices

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- **Protocol Technical Advisors**

1: Prepare Topic

2: Search for and Select Studies for Inclusion

3: Extract Data from Studies

4: Assess Quality of Individual Studies

- ++ Definitely Low risk of bias
- + Probably Low risk of bias
- Probably High risk of bias
- Definitely High risk of bias

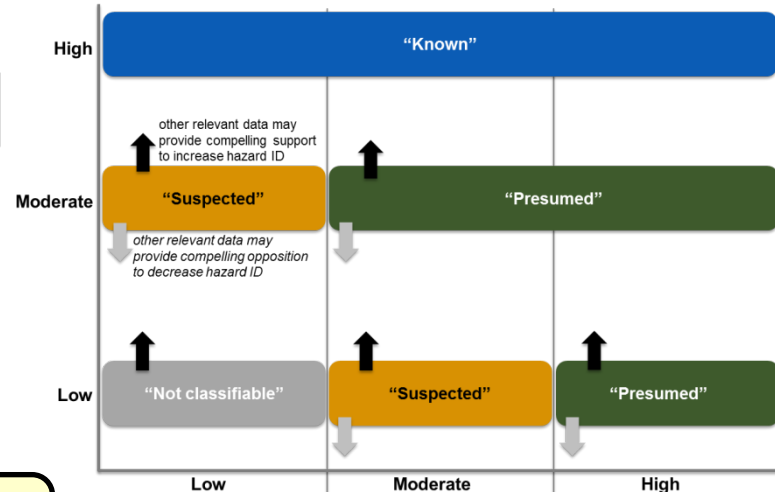
Questions?

5: Rate Confidence in the Body of Evidence

| Initial Confidence by Key Features of Study Design | Factors Decreasing Confidence | Factors Increasing Confidence | Confidence in the Body of Evidence |
|--|--|---|------------------------------------|
| High (++++) 4 Features | <ul style="list-style-type: none"> Risk of Bias Unexplained Inconsistency Indirectness Imprecision Publication Bias | <ul style="list-style-type: none"> Large Magnitude of Effect Dose Response All Plausible Confounding <ul style="list-style-type: none"> Studies report an effect and residual confounding is toward null Studies report no effect and residual confounding is away from null Consistency <ul style="list-style-type: none"> Across animal models or species Across dissimilar populations Across study design types Other <ul style="list-style-type: none"> e.g., particularly rare outcomes | High (++++) |
| Moderate (+++) 3 Features | | | Moderate (+++) |
| Low (++) 2 Features | | | Low (++) |
| Very Low (+) ≤1 Features | | | Very Low (+) |

7: Integrate Evidence to Develop Hazard ID Conclusions

of Evidence for Health Effect in Human Studies



Level of Evidence for Health Effects in Animal Studies

6: Translate Confidence Ratings into Evidence of Health Effects

| Confidence in the Body of Evidence | Direction (effect or no effect) | Level of Evidence for Health Effect |
|------------------------------------|---------------------------------|-------------------------------------|
| (+++ High) | Health effect | High |
| (++ Moderate) | Health effect | Moderate |
| (+ Low) | Health effect | Low |
| (+++ High) | No effect | Evidence of no health effect |
| (++ Moderate) | No effect | Inadequate |
| (+ Low) | No effect | Inadequate |

Extra Slides

Example Guidance in Protocols: When to Downgrade for Indirectness

Table 15. Guidance for downgrading human studies for directness

| Health outcomes | | Exposure scenario | Time between exposure and outcome assessment | Overall downgrade |
|-----------------|----|-------------------|--|-------------------|
| primary | 0 | 0 | 0 | 0 |
| secondary | -1 | 0 | 0 | -1 |

0 = no downgrade, -1 = one downgrade, -2 two downgrade

- 
- **Downgrade for secondary outcomes**

Example Guidance in Protocols: When to Downgrade for Indirectness PFOA / PFOS Exposure and Immunotoxicity

Table 16. Guidance for downgrading animal studies for directness

| Animal model | | Health outcomes | | Route of administration | | Time between treatment and assessment | Overall downgrade |
|---------------------------|----|-----------------|----|--|----|---------------------------------------|-------------------|
| Mammalian | 0 | primary | 0 | oral, sc injection, dermal, inhalation | 0 | 0 | 0 |
| | | | | intraperitoneal injection | -1 | 0 | -1 |
| | | secondary | -1 | oral, injection, dermal, inhalation | 0 | 0 | -1 |
| | | | | Intraperitoneal (ip) injection | -1 | 0 | -2 |
| Non-mammalian vertebrates | -1 | primary | 0 | oral, sc injection, dermal, inhalation | 0 | 0 | -1 |
| | | | | ip, water for aquatic species | -1 | 0 | -2 |
| Invertebrates | -2 | primary | 0 | | | | |
| | | secondary | -1 | | | | |

• **Route of administration**

Downgrade for Indirectness

• **Model (mammal=0, vertebrate -1, invertebrate -2)**

• **Health outcome (primary = 0, secondary -1)**

0 = no downgrade, -1 = one downgrade, -2 two downgrade

sc = subcutaneous, ip = intraperitoneal

Key Study Design Features for Initial Confidence

1. Exposure to the substance is controlled

- Experimental studies can largely eliminate confounding by randomizing allocation of exposure

2. Exposure assessment represents exposures occurring prior to the development of the outcome

- Supports causal pathway and if present, it is unlikely that association is the result of reverse causation

3. Outcome is assessed on the individual level (i.e., not population aggregate data)

- Without individual-level information on outcomes, a study cannot control for additional confounding variables (“ecologic fallacy”)

4. Comparison group is used within the study (e.g., not case reports)



Example Details Included in Summary Tables

Table 6 from PFOA/PFOS Exposure and Immunotoxicity Protocol

| Reference, Study Design & Population | Health Outcome | Exposure | Statistical Analysis | Results |
|--|--|---|---|--|
| (Carwile and Michels 2011) Study Design: cross-sectional Adults who participated in the 2003/04 and 2005/06 National Health and Nutrition Examination Survey (NHANES) and a spot urine sample analysed for BPA. N: 2747 Location: US, NHANES national survey Sex (% male): ♂ (49.6%) Sampling time frame: 2003-2006 Age: 18-74 years Exclusions: pregnant women, participants with missing urinary BPA, creatine, BMI, or covariate data Funding Source: NIH National Research Service (NRS-A) Author conflict of interest: not reported | Diagnostic and prevalence in total cohort: obesity: BMI ≥ 30 (n=932, 34.3%) overweight: 25 ≤ BMI < 30 (n=864, 31.8%) elevated waist circumference (WC): >102 cm in ♂ or ≥ 88 cm in ♀ (n=1330, 50%) *BMI = body mass index (kg/m ²) | Exposure assessment: urine (µg/g creatinine) ng/ml and creatinine as adjustment variable) measured by online SPE-HPLC-MS/MS (Ye 2005) Exposure levels: 2.05 µg/g creatinine (geometric mean), 1.18-3.33 (25-75th percentile) Q1: ≤1.1 ng/ml Q2: 1.2-2.3 ng/ml Q3: 2.4-4.6 ng/ml Q4: ≥ 4.7 ng/ml | obesity & overweight: polytomous regression elevated WC: logistic regression Adjustment factors: sex, age, race, urinary creatinine, education, smoking Statistical power: "appears to be adequately powered" based on ability to detect an OR of 1.5 with 80% power using Q1 prevalence of 40.4% obesity, 44.4% overweight, and 46% elevated WC | adjOR (95% CI) obesity Q2 vs Q1: 1.85 (1.22,2.79) Q3 vs Q1: 1.60 (1.02,2.44) Q4 vs Q1: 1.76 (1.06,2.94) overweight Q2 vs Q1: 1.66 (1.21,2.27) Q3 vs Q1: 1.26 (0.85,1.87) Q4 vs Q1: 1.31 (0.80,2.11) elevated WC Q2 vs Q1: 1.62 (1.11,2.36) Q3 vs Q1: 1.39 (1.02,1.90) Q4 vs Q1: 1.58 (1.03,2.42) |
| statistical power as "appears to be adequately powered" (sample size met), somewhat underpowered (sample size is 75% to <100% of recommended), "underpowered" (sample size is <75% of recommended), or "severely underpowered (sample size is <50% required) | | | | |
| RISK OF BIAS ASSESSMENT | | | | |
| Risk of bias response options for individual items: should we delete domains from this table? | | | | |
| Bias Domain | Criterion | | | Results |
| Selection | Was administered dose or exposure level adequately randomized? | n/a | not applicable | Analysis |
| | Was allocation to study groups adequately concealed? | n/a | not applicable | |
| | Were the comparison groups appropriate? | ++ | yes, based on quality of studies | |
| Confounding | Does the study design or analysis account for important confounding and modifying variables? | ++ | yes (sex, age, race, adjustment for nutrients) | Exposure |
| | Did researchers adjust or control for other exposures that are anticipated to bias results? | + | no, but not considered | |
| Performance | Were experimental conditions identical across study groups? | | | Health Outcome |
| | Did deviation from the study protocol impact the results? | | | |
| | Were the research personnel and human subjects blinded to the study group during the study? | | | |
| Attrition | Were outcome data incomplete? | | | (for any analysis) |
| Detection | Were the outcome assessors blinded to the study group? | | | Reference, Study Design and Population |
| | Were confounding variables controlled for? | | | |
| | Can we be confident in the results? | ++ | yes, NHANES methods are considered "gold standard" for urinary BPA | |
| | Can we be confident in the results? | ++ | yes, used standard diagnostic criteria | |
| Selective Reporting | Were all measured outcomes reported? | ++ | yes, primary outcomes discussed in methods were presented results section with adequate level of detail for data extraction | |
| Other | Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)? | ++ | none identified | |
| RISK OF BIAS | | 1 st Tier for risk of bias | | |
| Risk of bias response options for individual items: | | | | |
| ++ | definitely low risk of bias | | | |
| + | probably low risk of bias | | | |
| - | probably high risk of bias | | | |
| -- | definitely high risk of bias | | | |
| n/a | not applicable | | | |

Results

Analysis

Exposure

Health Outcome

Reference, Study Design and Population

Risk of Bias

Example Risk of Bias Details in Summary Table

Table 6 from PFOA/PFOS R

Reference, Study Design & Population
(Carwile and Michels 2011)
Study Design: cross-sectional
Adults who participated in the 2003/04 and 2006/07
National Health and Nutrition Examination Survey (NHANES) and a spot urine sample analysed for PFOA and PFOS
N: 2747
Location: US, NHANES national survey
Sex (% male): ♂ (49.6%)
Sampling time frame: 2003-2006
Age: 18-74 years
Exclusions: pregnant women, participants with missing urinary BPA, creatinine, BMI, or covariate data
Funding Source: NIH National Research Service Award
Author conflict of interest: not reported
statistical power as "appears to be adequately powered (sample size required), or "severe" underpowered (sample size

Risk of Bias

- Rating/answer to applicable questions
- Answers justified with text from study
- Hypothetical example on confounding:

“yes (sex, age, race urinary creatinine, education, smoking), but no adjustment for nutritional quality”

| RISK OF BIAS ASSESSMENT | | | |
|---|--|---------------------------------------|---|
| Risk of bias response options for individual items: should we delete domains from this table? | | | |
| Bias Domain | Criterion | Response | |
| Selection | Was administered dose or exposure level adequately randomized? | n/a | not applicable |
| | Was allocation to study groups adequately concealed? | n/a | not applicable |
| | Were the comparison groups appropriate? | ++ | yes, based on quartiles of exposure |
| Confounding | Does the study design or analysis account for important confounding and modifying variables? | ++ | yes (sex, age, race, urinary creatinine, education, smoking), but no adjustment for nutritional quality, e.g., soda consumption |
| | Did researchers adjust or control for other exposures that are anticipated to bias results? | + | no, but not considered to present risk of bias in general population studies |
| Performance | Were experimental conditions identical across study groups? | n/a | not applicable |
| | Did deviations from the study protocol impact the results? | + | no deviations reported |
| | Were the research personnel and human subjects blinded to the study group during the study? | n/a | not applicable |
| Attrition | Were outcome data incomplete due to attrition or exclusion from analysis? | + | not considered a risk of bias, excluded observations (≤ 87 for any analysis) based on missing BMI or covariate data |
| Detection | Were the outcome assessors blinded to study group or exposure level? | ++ | yes, BPA levels not known at time of outcome assessment |
| | Were confounding variables assessed consistently across groups using valid and reliable measures? | ++ | yes, used standard NHANES methods |
| | Can we be confident in the exposure characterization? | ++ | yes, NHANES methods are considered "gold standard" for urinary BPA |
| | Can we be confident in the outcome assessment? | ++ | yes, used standard diagnostic criteria |
| Selective Reporting | Were all measured outcomes reported? | ++ | yes, primary outcomes discussed in methods were presented results section with adequate level of detail for data extraction |
| Other | Were there any other potential threats to internal validity (e.g., inappropriate statistical methods)? | ++ | none identified |
| RISK OF BIAS | | 1 st Tier for risk of bias | |

| Risk of bias response options for individual items: | |
|---|------------------------------|
| ++ | definitely low risk of bias |
| + | probably low risk of bias |
| - | probably high risk of bias |
| -- | definitely high risk of bias |
| n/a | not applicable |